Cognitive Computing to Guide Molecular#Based Therapy Selection: Steps Forward amid Abundant Need

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Commentary

Cognitive Computing to Guide Molecular-Based Therapy Selection: Steps Forward amid Abundant Need

Leif W. Ellisen

Massachusetts General Hospital Cancer Center, Boston, Massachusetts; Harvard Medical School, Boston, Massachusetts

Disclosures of potential conflicts of interest may be found at the end of this article.

This is an exciting time for clinical and translational oncology. Revolutionary advances in DNA sequencing technology have paralleled the growth of gene- and pathway-targeted therapeutics, resulting in more rational, efficient, and effective drug development pipelines centered on tumor-specific genetic abnormalities. The need to enhance this paradigm by expanding the genetic information we obtain from patients' tumors is self-evident. At the same time, the number of available therapeutic agents and combinations will continue to grow. All this progress provides extraordinary opportunities for identifying more and better treatment approaches for cancer patients. Nonetheless, the parallel growth of tumor mutational information and mutation-associated therapeutic options is outpacing the ability of individual practitioners to reliably identify these options. This challenge has led to the organization of "Molecular Tumor Boards" (MTBs), groups of scientists and clinicians who routinely review patient-level tumor genetic information and make recommendations for therapeutic actions. Useful as they may be, however, the MTBs generally rely on a handful of experts whose own knowledge base is neither comprehensive nor continuously up to date. Collectively, these facts set the stage for the study by William Kim and colleagues published in this issue [1], which sought to apply cognitive computing to the challenge of matching individual patients to available therapies based on tumor DNA sequencing data.

The authors' approach involved a retrospective review of 1,018 cases that had undergone tumor sequencing. A head-to-head and contemporaneous comparison was performed of recommendations provided by the local University of North Carolina (UNC) MTB with those provided by the Watson for Genomics (WfG) cognitive computing platform. Recommended matches could involve an approved drug and indication, an off-label indication of an approved drug, or a clinical trial. The bottom line findings of the study were that WfG identified all "actionable" genetic mutations identified by the local MTB, but it also identified additional actionable mutations in 323 patients. Essentially all of the WfG additional findings related to mutations in eight genes that were not on the UNC MTB list of actionable alterations at the time of the review, but were deemed actionable by WfG due to recent publications and/or recently opened clinical trials of agents in the relevant pathways. Notably, because of its retrospective nature, the study could not systematically address whether the matching information led to the recommended action, or whether the patient benefitted as a result.

How much of a step forward do these findings represent, and what are the next steps required to further advance informatics support systems such as WfG? Answering these questions first requires being explicit about what we would like such systems to do. As discussed in the manuscript by Kim et al., at least three distinct components are involved in identifying actionable alterations following initial sequence analysis. The first is determining whether an individual gene mutation is actually function-altering. This determination is far from trivial and often requires integration of protein modeling data, in vitro data, and clinical data, to the extent that these exist for the sequence variant in question. The present study did not specifically credential the validity of variant-calling by WfG, and in any case, none of the newly actionable determinations involved changes in variant calling. The second component in the analysis is the assignment of a given altered gene to a specific functional pathway. Again, this is a complex endeavor that should not be based simply on canonical pathway concepts, but ideally must integrate emerging data on cross-talk and dynamic feedback between and within pathways [2, 3]. Finally, each available therapeutic agent must be assigned to relevant pathway(s), given that much of the matching does not involve the mutant gene itself as the therapeutic target, but rather the resulting altered pathways.

Each of these components will need to be formally validated if informatics platforms such as WfG are to prove maximally useful. Indeed, recent examples suggest that suboptimal matching of genes to pathways and pathways to drugs may lead to therapeutic interventions that provide little or no benefit to patients. For example, the SHIVA trial randomized patients to therapy matched to the tumor molecular profile versus physician's choice standard therapy. Fully 59% of patients (293/496) who had complete molecular profiles were found to have a therapeutic match. Unfortunately, matched therapy provided no advantage in overall progression-free survival (PFS) compared with physician's choice therapy [4]. Among the possibilities raised to explain the failure of this trial to demonstrate an advantage for matched therapy was inaccurate or promiscuous matching. Potentially supporting this interpretation are the

Correspondence: Leif W. Ellisen, M.D., Ph.D., Massachusetts General Hospital Cancer Center, CPZN 4204, 185 Cambridge Street, Boston, Massachusetts 02114, USA. Telephone: 617-726-4315; e-mail: lellisen@mgh.harvard.edu Received December 11, 2017; accepted for publication December 14, 2017; published Online First on January 12, 2018. http://dx.doi.org/10.1634/theoncologist.2017-0653

findings of the subsequent MOSCATO trial, which compared PFS on matched therapy with that achieved with the patient's prior line of therapy. Only 49% of profiled patients (411/843) were assigned a match, and yet MOSCATO did demonstrate significantly longer PFS on matched compared with prior therapy [5]. Although the design of SHIVA and MOSCATO were substantially different, the overall results underscore that finding a match is not an end unto itself, but only a means of testing the possibility of benefit.

In the study by Kim et al., 70% of patients (703/1,018) were initially found to have one or more actionable matches by the UNC MTB, and an additional 96 patients without a prior match were matched to therapy by WfG. Thus, the final proportion of patients with a reported match in the study was a remarkably high 78%. Furthermore, a substantial number of patients had multiple matches, raising the issue of how effectively WfG (and the MTB) were able to prioritize the matches. The extent to which these relatively high rates of matching and their subsequent prioritization would translate into clinical efficacy are critical questions for future studies.

Even if we accept the premise that all the described analysis steps worked optimally, the findings of Kim et al. largely demonstrate that the current WfG platform can provide more up-to-date analysis of single genes linked to sensitivity and potentially to resistance. Thus, the advantage compared with the MTB approach is a quantitative one—more efficient processing of data—rather than a qualitative one—identifying new patterns that are unlikely to emerge from human-based analyses. Clearly, however, as tumors are divided into ever-smaller molecular subsets based on not just single mutations but combinations thereof, the ability of humans to recognize clinically relevant patterns will become even more limited. The same is true for effects of new drug combinations. Thus, a truly useful cognitive computing platform must take us out of the realm of "known unknowns"—the availability of drugs to target the genes and pathways whose alterations we recognize and understand at some level—and into the exciting area of "unknown unknowns"—the pathway alterations and drug effects that are unanticipated and might only be gleaned through sophisticated integration of large and complex datasets.

Despite these caveats, the Kim study does indeed point to immediate and potential highly impactful applications of cognitive computing platforms. Although MTBs may be up to date at the time of initial patient presentation, most MTBs are not equipped to systematically reanalyze patient data looking for new matches. In contrast, this study demonstrates that such a procedure is trivial for a computational algorithm such as WfG. The concept that each patient's tumor molecular profile could be continuously scanned for matches based on all available data should be an exciting one for both patients and clinicians. Ultimately, the growing complexity of oncology clinical and translational research demands the integration of such informatics support platforms. Accordingly, even small steps help us envision a future in which established paradigms and new findings and opportunities can be integrated more effectively, ultimately yielding a research enterprise that is far more sophisticated than the sum of its parts.

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Editor's Note:
See the related article, "Enhancing Next-Generation Sequencing-Guided Cancer Care Through Cognitive Computing," by William Y. Kim et al., on page 179 of this issue.